**Case:** A lean 22 y/o woman is hirsute and has oligomenorrhea. She presents because of infertility (the absence of pregnancy after 1 year of regular, unprotected sex). *What is in the differential diagnosis of infertility in a hirsute woman?* 

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Learning objectives

At the conclusion of this presentation, the laboratorian will be able to:

- List a differential diagnosis of hirsutism and infertility
- Classify and differentiate the different varieties of CAH
- Diagnose and treat late-onset CAH
Differential diagnosis of infertility in a hirsute woman:

Polycystic ovarian syndrome (PCOS; associated w/ MS)
Medications (e.g., danazol for endometriosis)
Late-onset congenital adrenal hyperplasia
Cushing syndrome
Androgen secreting tumors (ovarian or adrenal)

Precocious adrenarchy (early-onset axillary and/or pubic hair)
What is congenital adrenal hyperplasia (CAH)?

(I) Inborn error in steroid biosynthesis: variable impairment in the synthesis of:

~ Cortisol (alone)
   (or)
   Cortisol & Aldosterone

(II) Disordered adrenal androgen production

- Shared biosynthetic pathways w/ testes & ovary

- Adrenal androgens: precursors of estrogens
  precursors of androgens
What are the consequences of disordered *adrenal androgen* synthesis in congenital adrenal hyperplasia (CAH)?

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Excess</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In utero</td>
<td>Genital hyperpigmentation</td>
<td>Virilization -- &gt; 46,XX DSD</td>
</tr>
<tr>
<td>Ex utero</td>
<td>Precocious puberty</td>
<td>Accelerated growth (children); virilization</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Testosterone deficiency</strong></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>In utero</td>
<td>Inadequate virilization 46,XY DSD</td>
<td>No adverse effect</td>
</tr>
<tr>
<td>Ex utero</td>
<td>46,XY DSD</td>
<td>No adverse effect</td>
</tr>
</tbody>
</table>
What is the most common form of congenital adrenal hyperplasia (CAH)?

Def. of 21-alpha hydroxylase (21-OHylase)

- Formal gene name: **CYP21A2**

*Cytochrome P450, Family 21, Subfamily A, Polypeptide 2
CYP21A1P = Cytochrome P450, Family 21, Subfamily A, Polypeptide 1 Pseudogene*
What regulates the expression of 21-OHylase?

CRH

++

Hypothalamus

++

Anterior pituitary (corticotrophs)

ACTH

-

Adrenal cortex (fasciculata & reticularis)

Cortisol

**Enzymes regulated by ACTH**

- StAR
- 20,22 desmolase* (CYP11A)
- 17-OHylase (CYP17)
- 3-beta HSD
- 21-OHylase (CYP21A2)
- 11-beta hydroxylase (CYP11B1)

StAR = steroid acute regulatory protein; transports chol into adrenal cortical cells; * a.k.a. – side-chain cleavage enzyme.

(1) Excellent data for their regulation by ACTH
What are the consequences of adrenal steroid hormone deficiency?

<table>
<thead>
<tr>
<th><strong>Hormone def.</strong></th>
<th><strong>Consequences:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol</td>
<td>Lack energy, N/V, weight loss, hypoglycemia, hyponatremia, vascular collapse, hypotension, shock, death</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>Hyponatremia, hyperkalemia, acidosis, hypovolemia, hypotension, shock, death</td>
</tr>
</tbody>
</table>
What is the biochemistry of 21-OHylase def.?
21-alpha hydroxylase deficiency (dashed line), there is cortisol deficiency and there may be aldosterone deficiency. Elevations in 17-hydroxy progesterone and androstenedione are observed.
What are other forms of CAH?

Other types of CAH:

11-beta hydroxylase def.

17-alpha hydroxylase def.

3-beta hydroxy steroid dehydrogenase def. (3-beta HSD def.)

Lipoid CAH [steroidogenic acute regulatory (StAR) protein def.]
What is the range of consequences of 21-OHylase def.?

<table>
<thead>
<tr>
<th>Severity</th>
<th>Classification</th>
<th>Phenotype of 21-OHylase CAH</th>
<th>Age of onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>++++</td>
<td>Classical</td>
<td>Salt-wasting</td>
<td>Newborns</td>
</tr>
<tr>
<td>+++</td>
<td>Classical</td>
<td>Simple virilizing</td>
<td>Newborns</td>
</tr>
<tr>
<td>++</td>
<td>Nonclassical*</td>
<td>Late-onset</td>
<td>Late childhood, adolescence or adulthood</td>
</tr>
<tr>
<td>+</td>
<td>Heterozygous carrier</td>
<td>Asymptomatic</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Attenuated;  N/A = not applicable
Non-classical CAH

Unaffected (not a carrier)

Classical CAH

Heterozygotes (+/- NI basal 17-OHP)
What is effect of *salt-wasting* or *simple virilizing* CAH on the development of the external genitalia in the 46,XX fetus?

Excess adrenal androgens
(androstenedione & DHEA)

Virilization of external genital

Disorder of sexual development (DSD)
[46,XX, DSD]
How do salt-wasting and simple virilizing CAH differ?

<table>
<thead>
<tr>
<th></th>
<th>DSD</th>
<th>Cortisol def.</th>
<th>Aldosterone def.</th>
<th>Addisonian crisis (if untx’ed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salt-wasting</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Simple virilizing</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
What is the epidemiology of late-onset of 21-OHylase def.?

**Hz:** 1 in 1000

**Incr. Hz in:** Ashkenazi Jewish, Mediterranean, Middle-Eastern and Indian populations

**Note:** Dx may be missed in boys
What is the **phenotype** of late-onset of 21-OHylase def. in females?

**Androgen excess:**
- Hirsutism (59%), acne (33%), androgenic alopecia, anovulation, menstrual dysfunction (54%: oligomenorrhea) & infertility

**Prepubertal:**
- +/- Tall stature, advanced skeletal maturation, and premature development of pubic hair, axillary hair, and adult apocrine odor; +/- clitororomegaly

**Women:** Polycystic ovary-like phenotype

*Note: Boys may have penile enlargement with prepubertal testes.*
How is the diagnosis of late-onset CAH established?

Compatible clinical history of androgen excess:

**Girls**: +/- premature adrenarche, accelerated growth

**Girls, adolescents/women**: acne, hirsutism

**Adolescents/women**: menstrual dysfunction & infertility

Elevated basal and 60 min. post-ACTH 17-OHP
Other hormone measurements in late-onset CAH

T = Testosterone
A = Androstenedione
DHA-S = Dehydroepiandrosterone sulfate
$3\alpha$ Diol = Urinary $3\alpha$-androstanediol glucuronide*
$5\alpha$ reductase = Activity of T $\rightarrow$ DHT converting enzyme

* Marker of peripheral androgen metabolism
What are complications of late-onset of 21-OHylase def.?

Adrenal tumors

Adrenal hypertrophy

Adrenal myolipoma (rare)
What is in the *differential diagnosis* of late-onset of 21-OHylase def.?

**Conditions producing hirsutism and/or menstrual irregularities (including infertility)**

- Polycystic ovarian syndrome (PCOS)
- Medications (e.g., danazol for endometriosis)
- Cushing syndrome
- Androgen secreting tumors (ovarian or adrenal)
- Precocious adrenarchy (early-onset axillary and/or pubic hair)
How can hirsutism be evaluated (not exhaustive)?

- Regular Menses
  - Idiopathic
    - Tumor
      - HAIR-AN (type A ins.res., IR or post-IR mutations)
  - Suddenly irregular, severe and/or rapid
  - Chronic irregular
    - Obese
      - PCOS (metabolic syndrome)
    - Non-obese
      - Late-onset CAH

HAIR-AN syndrome is defined as a constellation of hyperandrogenism (HA), insulin resistance (IR), and acanthosis nigricans (AN).
How is late-onset of 21-OHylase def. excluded from the differential diagnosis of hirsutism or menstrual irregularity (including infertility)?

17-OHP
- Basal &
- Post-ACTH

Normal  Elevated

Late-onset CAH  Late-onset CAH
Ruled out  Ruled in
<table>
<thead>
<tr>
<th><strong>How and when should late-onset of 21-OHylase def. be treated? (1)</strong></th>
<th><strong>Girls &amp; boys</strong></th>
<th><strong>Treatment</strong></th>
<th><strong>Goal</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Girls &amp; boys</td>
<td>W/ pre-, early puberty ( +)</td>
<td>Glucocorticoids ( +/- GnRH agonist for precocious puberty)</td>
<td>Decr. rate of skeletal maturation incr. final height</td>
</tr>
<tr>
<td>Pubertal girls</td>
<td>ACTH-stimulated Cortisol: &lt;18 mcg/dL</td>
<td>Glucocorticoids</td>
<td>Tx glucocorticoid def.; prevent Addisonian crisis</td>
</tr>
<tr>
<td></td>
<td>=&gt; 18 mcg/dL</td>
<td>Glucocorticoids</td>
<td>Tx at times of stress; prevent Add.crisis</td>
</tr>
</tbody>
</table>

BA = bone age
How should late-onset of 21-OHylase def. be treated in adult women? (2)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral contraceptives *</td>
<td>+/- decr. ovarian androgen secretion, improve acne, slow hirsutism, restore menstrual cyclicity</td>
</tr>
<tr>
<td>Antiandrogens*</td>
<td>+/- helpful for hirsutism and androgenic alopecia</td>
</tr>
</tbody>
</table>

* spironolactone, flutamide, cyproterone acetate, or finasteride
SUMMARY

Classical 21-OHylase CAH

Fetus -- > virilization: 46, XX DSD

Newborn: +/- Addisonian crisis
- salt-losing versus simple virilizing

Late-onset CAH (nonclassical CAH): common disorder

Presents as hirsutism, menstrual irregularity, infertility

Men: ~asymptomatic

Tx. w/ glucocorticoids if low cortisol response to ACTH
THE END